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Preferential Solvation of Neutral Species in Binary Solvent Mixtures Characterized by 1H NOESY NMR Spectroscopy

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When a substance is dissolved in a mixture of solvents, if the composition of its solvation shell is different from that of the bulk solution, the solute is said to be preferentially solvated by one cosolvent.[1] Preferential solvation (PS) arises commonly, and because it modifies the neighborhood of the solute, it affects its conformation and reactivity.[2−9] Although PS has been investigated with a variety of methods (electrochemical,[10] thermodynamic,[11] UV-vis,[12−14] IR,[15] and NMR[16−18]), most studies have been directed to electrolyte solutions;[19] whereas, simple organic molecules have received attention only recently.[11,20,21] Moreover, most methods developed are rather specific. We have probed the PS of neutral organic species from intermolecular 1H NOESY measurements, interpreting the results by means of Macura−Ernst theory to yield the preferred solvent.

For small molecules in nonviscous solvents, the intermolecular dipole−dipole contribution depends on the reciprocal distance, the mutual translational diffusion of the interacting species, and on the spin concentration that the solvent can furnish;[22,23] all of these quantities are related to solvation. In a NOESY spectrum, off-diagonal peaks arise from dipolar cross-relaxation among interacting spins; hence, intermolecular cross-peaks yield information on the efficiency of solute−solvent dipolar cross-relaxation. In order to relate this with the composition of the solvation shell, we have made use of the theory developed by Macura and Ernst,[24] later reviewed by Perrin,[25] which allows one to calculate the intensity of inter-molecular NOESY crosspeaks.

If we denote the solute with A and the two solvents with B and C, the ratio of crosspeaks due to each individual solute−solvent interaction (a_{AB}/a_{AC}) will be given by eq 1

$$\frac{a_{AB}}{a_{AC}} = \frac{n_B}{n_C} \frac{\exp(-\mathbf{R}\tau_m)_{AB}}{\exp(-\mathbf{R}\tau_m)_{AC}} \tag{1}$$

where n_i (i = B, C) are the spin concentrations provided by the solvents, $\mathbf{R}$ is the relaxation matrix (which contains cross-relaxation rates), and $[\exp(-\mathbf{R}\tau_m)]_{Ai}$ is the matrix element corresponding to the interaction between the spins of solute A and solvent i.[26] Macura and Ernst, for the sake of simplicity, provided theoretical expressions for $\mathbf{R}$ under the constraint of equal relaxation efficiency for all interacting pairs, which is unsuitable for the present purpose. Consequently, we modified the original expressions to account for this.[26]

Values of a_{AB}/a_{AC} are calculated by setting all spin concentrations to the values dictated by the composition. If there is preferential solvation, this will be reflected in a different experimental a_{AB}/a_{AC} ratio. Thus, if $(a_{AB}/a_{AC})_{exptl} > (a_{AB}/a_{AC})_{calcd}$, solute A will be preferentially solvated by solvent B rather than by C, and vice versa.

We have investigated phenol and *N*-methylbutyramide (NMBA) as solutes in CH_3CN/H_2O, $DMSO/H_2O$, Et_2O/CH_2Cl_2 (phenol), and CH_3CN/H_2O, 1,4-dioxane/benzene (NMBA); the solute (A) was kept at low concentration ($x_A \approx 0.02$), the two cosolvents B and C being at equal mole fraction of ca. 0.5.[28] Owing to the small molecular weight of the species studied, T_1 values are rather long, which entails long mixing times. A sample spectrum is shown in Figure 1. Integrals of crosspeaks were then evaluated as the sum of the volumes of all signals, yielding $(a_{AB}/a_{AC})_{exptl}$, and are compared with $(a_{AB}/a_{AC})_{calcd}$ (obtained from eq 1) in Table 1.

Table 1 shows that in almost all cases $(a_{AB}/a_{AC})_{exptl}$ differs appreciably from the calculated value. One can then infer, within the scope of the model adopted, that phenol in CH_3CN/H_2O and $DMSO/H_2O$ is preferentially solvated by the organic cosolvent and shows a weak preference for CH_2Cl_2 over Et_2O. Likewise, NMBA in CH_3CN/H_2O shows a marked preference for CH_3CN, and in 1,4-dioxane/C_6H_6 it is preferentially solvated by C_6H_6. These findings can be explained by noting that CH_3CN can solvate phenol both by hydrogen bonding and (unlike

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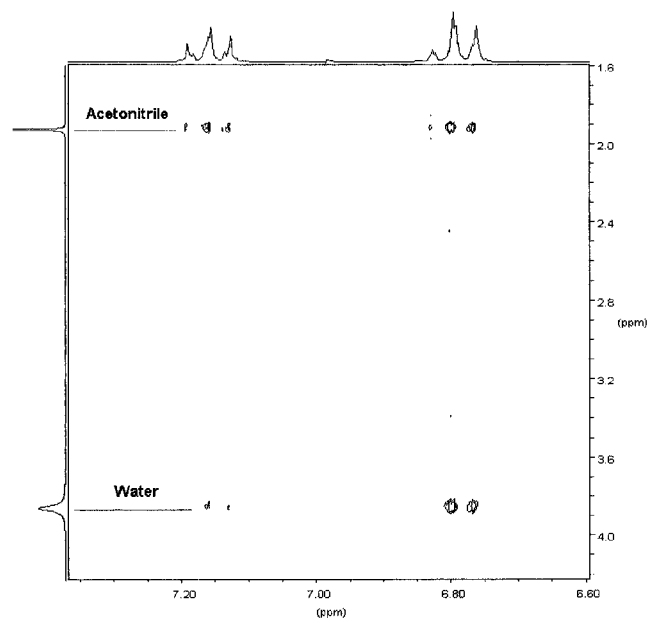
Figure 1. Aromatic region of the 250 MHz phase-sensitive (TPPI mode) ^{1}H NOESY spectrum of phenol in CH$_3$CN/H$_2$O (degassed solution at 25 °C). Spectral window in ν_2 1730.1 Hz, 8K data points, 48 scans; 204 experiments, zero-filled to 1024; mixing time 7 s (average T_1 in the system); total time ca. 60 h.

Table 1. Experimental and Calculated Values of the Ratio of Intermolecular NOESY Crosspeaks[a]

solute (A)	solvent		τ_m (s)	(a_{AB}/a_{AC})	
	(B)	(C)		calcd	exptl
phenol	H$_2$O	**CH$_3$CN**	7.0	2.22	1.48
phenol	H$_2$O	**DMSO**	3.4	1.55	1.03
phenol	**CH$_2$Cl$_2$**	Et$_2$O	10.0	0.49	0.59
NMBA	H$_2$O	**CH$_3$CN**	4.0	2.14	1.09
NMBA	1,4-dioxane	**C$_6$H$_6$**	2.9	1.09	0.52

[a] The preferred solvent is highlighted in boldface.

water) by London dispersion interactions; for phenol in DMSO/H$_2$O, DMSO is the preferred solvent owing to its stronger hydrogen bond acceptor properties. Both results in fact agree with the enthalpies of solution of phenol[29] (ΔH_s = +2.7, +2.4, −0.7 kcal/mol in H$_2$O, CH$_3$CN, and DMSO, respectively), i.e.,

the preferred solvent has the most exothermic ΔH_s. On the other hand, ΔH_s values in CH$_2$Cl$_2$ and Et$_2$O are not available for comparison. For NMBA, our results indicate that in both CH$_3$-CN/H$_2$O and dioxane/C$_6$H$_6$ mixtures the amide prefers the least "polar" solvent (CH$_3$CN and C$_6$H$_6$, respectively). These results seem contrary to the common notion of amides as hydrophilic compounds. However, for phenol, CH$_3$CN can also stabilize the aliphatic chain of CH$_3$CH$_2$CH$_2$C(O)NHCH$_3$ by London dispersion interactions, while water cannot. Hence, our results point out that the solvation properties of "side chains" may actually overwhelm those of functional groups which are often regarded as the focus of solvation.

Owing to the scarcity of literature data on analogous systems, any comparison is narrow in scope. Wakisaka et al. recently devised an elegant method based on determining the composition of molecular clusters obtained by rapid evaporation of droplets of the solution under study by mass spectrometry.[21] When applied to a solution of phenol in CH$_3$CN/H$_2$O, this method afforded the conclusion that phenol is preferentially solvated by CH$_3$CN, in agreement with our results. Similarly, in the DMF/H$_2$O/n-PrOH system,[11a] studied by Matteoli et al. by means of Kirkwood−Buff integrals, DMF showed no appreciable preference for either solvent, which was explained in terms of a competition between hydrophobic interactions with propanol and HB with water; hence, again an amide did not show a marked preference for water over an organic cosolvent.

We have thus demonstrated that intermolecular NOESY spectra can be employed to yield the structure of the solvation shell in mixed solvents, which agrees with existing experimental data or is otherwise chemically consistent. When compared to other methods, intermolecular NOESY spectra offer the advantages of being generally applicable and of requiring commonly available instrumentation. The extension of these measurements to other cases and more complex systems is currently underway.

Supporting Information Available: Calculation of the relaxation matrix (2 pages). See any current masthead page for ordering and Internet access instructions.

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